Remarks

Reconsideration of this Application is respectfully requested. Applicant respectfully requests entry of this reply and accompanying evidence after a final Office Action because the reply is filed concurrently with a Request for Continued Examination under 37 C.F.R. § 1.114. *See* 37 C.F.R. § 1.116(a).

Claims 1, 4, 6, 8 and 11 are pending in the application, with claims 1 and 8 being the independent claims.

Based on the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding rejection and that it be withdrawn.

Rejection Under 35 U.S.C. § 103

In the Office Action, the Examiner maintained the rejection of claims 1, 4, 6, 8 and 11 under 35 U.S.C. § 103(a), as allegedly obvious over Seymour, A., *Manag. Care, 10*:11-16, 2001 (hereinafter "Seymour") in view of McCall, A.L., *Expert Opin. Pharmacother. 2*:699-713, 2001 (hereinafter "McCall"). Applicant respectfully traverses the rejection for at least the reasons of record and the additional reasons that follow.

Legal Principles

Obviousness determinations under 35 U.S.C. § 103 are carried out according to the standard set forth by the United States Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966):

> [u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc.,

> might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Id. at 17-18, 148 U.S.P.Q. at 467.

In proceedings before the U.S. Patent and Trademark Office (USPTO), the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 U.S.P.Q. 785, 787-88 (Fed. Cir. 1984). Additionally, there must be a reason or rationale behind an obviousness determination and "this analysis should be made explicit." *See KSR International Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1741 (2007) (citing *In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.")).

In response to *KSR*, the USPTO issued "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" 72 Fed. Reg. 195, pp. 57526-35 (October 10, 2007) (hereinafter "2007 *KSR* Guidelines"). The 2007 *KSR* Guidelines reiterate and emphasize the Examiner's role as a fact finder, using the factual inquiries set forth in *Graham*. Based on the fact record, the Examiner must use "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." 2007 *KSR* Guidelines at page 57529 (internal citation omitted).

On September 1, 2010, the USPTO issued "Examination Guidelines Update: Development in the Obviousness Inquiry After *KSR* v. *Teleflex*." 75 Fed. Reg. 169, pp. 53643-60 (hereinafter "2010 *KSR* Guidelines Update"). The 2010 *KSR* Guidelines

Update provides reviews of several Federal Circuit cases that have involved the application of the law of obviousness since *KSR* to assist USPTO patent examiners, as discussed in further detail below.

Seymour and McCall do not teach a composition comprising a synergistic combination of glimepiride and metformin hydrochloride at the specified weight ratios.

The present claims recite a solid pharmaceutical composition comprising a synergistic combination of glimepiride and metformin hydrochloride, wherein the weight ratio of glimepiride and metformin hydrochloride is about 1/500 (claim 1), or a method of controlling blood glucose levels in a patient with type 2 diabetes, comprising administering to said patient a synergistic combination of glimepiride and metformin hydrochloride, in a solid dosage form, wherein the weight ratio of glimepiride and metformin hydrochloride is about 1/500 (claim 8). Claims 4 and 6 depend from claim 1, and claim 11 depends from claim 8. The dependent claims are patentable for at least the reasons set forth for claims 1 and 8 below.

Seymour provides a clinical overview for the treatment of diabetes with glyburide and metformin hydrochloride as an initial therapy or as a replacement therapy for patients who are inadequately controlled on monotherapy. *See, e.g.*, Seymour at page 16. Seymour further provides recommended Glucovance® (glyburide and metformin hydrochloride) starting doses for initial and replacement therapy (Table 2) and a conversion guide for switching patients, for example, from Amaryl® (glimepiride) and Glucophage® (metformin hydrochloride) dual therapy to Glucovance® (Table 1). As such, Seymour does not teach a composition comprising both glimepiride and metformin hydrochloride in the same composition. In addition, Seymour does not teach the claimed

synergistic combination of glimepiride and metformin hydrochloride, as noted by the Examiner. *See* Office Action at page 4.

The Examiner relies on the disclosure of McCall to cure these deficiencies, asserting that McCall teaches, for example, that: (1) glimepiride is approved for use with metformin; (2) glimepiride can be given at a dose of 1-8 mg as a monotherapy; and (3) glimepiride may have certain advantages over glyburide. *See* Office Action at page 5. However, McCall does not cure the deficiencies of Seymour because it does not teach a composition comprising both glimepiride and metformin hydrochloride in the same composition, let alone a composition comprising a synergistic combination of glimepiride and metformin hydrochloride at the specified weight ratios. Thus, for at least these reasons, Seymour and McCall cannot be used to support a *prima facie* case of obviousness of the claims.

Seymour teaches away from the use of glimepiride and metformin hydrochloride together.

When references teach away from making a claimed combination, there can be no expectation of success in combining the references to support a *prima facie* case of obviousness. *See* 2007 *KSR* Guidelines at page 57529. As described above, Seymour provides recommended Glucovance® (glyburide and metformin hydrochloride) starting doses for initial and replacement therapy (Table 2) and a conversion guide for switching patients, for example, from glimepiride and metformin hydrochloride dual therapy to Glucovance® (Table 1). As such, Seymour teaches *switching* patients from glimepiride and metformin hydrochloride dual therapy to glyburide and metformin hydrochloride therapy, and therefore teaches away from glimepiride and metformin hydrochloride

therapy. Accordingly, for at least these reasons, Seymour cannot be used to support a *prima facie* case of obviousness of the claims.

The Examiner has not provided the requisite rationale for why the claimed subject matter would have been obvious over Seymour in view of McCall.

In explaining the obviousness rejection, the Examiner asserts that it would have been obvious to substitute the glyburide component disclosed in Seymour with the glimepiride component disclosed in McCall, because it was known that glimepiride was associated with reduced hypoglycemic adverse effects. *See* Office Action at page 5. In addition, the Examiner asserts that one would have been motivated to combine the references because of the "individually known common utility" of the components of the references. Office Action at page 6. Regardless of whether or not one would have been motivated to substitute glyburide with glimepiride, Applicant submits that one of ordinary skill in the art at the time the present application was filed would not have expected such a substitution would result in a synergistic combination of glimepiride and metformin hydrochloride, because, as mentioned above, Seymour and McCall do not teach or suggest the claimed synergistic combination of glimepiride and metformin hydrochloride. In addition, art available at the time the present application was filed confirms that one of ordinary skill in the art would not have expected the claimed glimepiride and metformin hydrochloride composition would result in a synergistic combination. For example, De Fronzo, R.A., *Ann. Intern. Med., 131*:281-303, 1999 (provided as document NPL8 in the Information Disclosure Statement filed on August 24, 2009) discloses that clinical trials had not demonstrated the superiority of one sulfonylurea over another when given in maximally effective doses, and that clinical

trials had shown glyburide and glimepiride exert equipotent glucose-lowering effects. *See, e.g.,* De Fronzo at page 289.

In explaining the obviousness rejection, the Examiner further asserts that it would have been obvious to a person of skill in the art at the time the invention was made to substitute the glyburide component of Glucovance® as taught by Seymour with glimepiride as taught by McCall because "...it is routine in the medical arts to combine drugs that are known to have the same therapeutic utility and both metformin hydrochloride and glimepiride are known hypoglycemic drugs...." Office Action at page 6. As such, the Examiner's rationale relies primarily on the assertion that a person of ordinary skill in the art would substitute glimepiride from all available sulfonylurea agents in a formulation containing metformin hydrochloride, and would then determine alternative dosages of metformin hydrochloride and glimepiride to arrive at dosages within the claimed weight ratios, because such dosages were individually known.

A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *See* M.P.E.P. § 2143.01; *Ex parte Levengood,* 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993). "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR,* 82 U.S.P.Q.2d at 1396 quoting *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006).

Furthermore, it is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection is based. *See* M.P.E.P. § 2144.03(a); *In re Zurko*, 258 F.3d 1379, 1385 (Fed. Cir. 2001) ("[T]he Board cannot simply reach conclusions based on its own understanding or experience-or on its assessment of what would be basic knowledge or common sense. Rather, the Board *must point to some concrete evidence* in the record in support of these findings." (emphasis added)). As the court held in *Zurko*, an assessment of basic knowledge and common sense that is not based on any evidence in the record lacks substantial evidence support. *Id.* In addition, the U.S. Supreme Court has held that "rejections on obviousness cannot be sustained by *mere conclusory statements*; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR,* 82 U.S.P.Q.2d at 1396 quoting *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006).

Applicant respectfully submits that the Examiner has not provided evidence in the record that one of ordinary skill in the art would arrive at a synergistic combination of glimepiride and metformin hydrochloride at the specified weight ratio in view of the cited references. Rather, Applicant respectfully asserts that the Examiner has simply made an unsupported, conclusory statement that cannot and does not support a *prima facie* case of obviousness. *See KSR,* 127 S.Ct. at 1741. To combine references without evidentiary support constitutes impermissible hindsight. *See KSR,* 127 S. Ct. at 1740-41 ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art."). Applicant respectfully submits that the Examiner has used impermissible hindsight to arrive at the conclusion

that the claims are obvious over Seymour in view of McCall and has therefore not established a *prima facie* case of obviousness.

M.P.E.P. § 2141 provides exemplary rationales that may support a conclusion of obviousness. Of those, it appears that the Examiner may be alleging that the claimed subject matter was "obvious to try" because one of ordinary skill in the art purportedly could choose from a finite number of identified, predictable solutions in the art with a reasonable expectation of success. *See* M.P.E.P. § 2141(III)(E). Applicant respectfully disagrees that the claimed synergistic combination of glimepiride and metformin hydrochloride at the specified weight ratio would be predictable, as detailed below.

For at least these reasons, Applicant submits that the Examiner has not established a *prima facie* case of obviousness over the cited references, and therefore respectfully requests that this rejection be withdrawn.

Obviousness of the claimed subject matter cannot be predicated on an unknown or allegedly inherent property of the art.

Obviousness cannot be based on unknown properties of a composition. *See In re Ehrreich*, 590 F.2d 902, 909 (C.C.P.A. 1979) ("The question in a § 103 case is what the references would collectively suggest to one of ordinary skill in the art."); *see also In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966). "That which may be inherent is not necessarily known . . . [and] [o]bviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d at 448; *see also In re Adams*, 356 F.2d 998 (C.C.P.A. 1974). The law of anticipation by inherency, *i.e.*, lack of novelty, must be clearly distinguished from the law of obviousness. *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984). "[T]hough anticipation is the epitome of obviousness, [anticipation and obviousness] are separate and distinct concepts." *Id.*

At page 7 of the Office Action, the Examiner alleges that, because the art encompasses a fixed dose combination comprising glimepiride and metformin hydrochloride in a weight ratio of 1/500, and the claims encompass a fixed dose combination comprising glimepiride and metformin hydrochloride in a weight ratio of 1/500, one would reasonably expect that a combination comprising glimepiride and metformin hydrochloride in a weight ratio of 1/500 would exhibit "a synergistic combination." As explained above, Applicant disagrees that the art cited by the Examiner encompasses a fixed dose combination comprising both glimepiride and metformin at the claimed ratio. Moreover, the Examiner appears to allege that the synergistic combination of the claimed compositions is an inherent property of a composition comprising glimepiride and metformin hydrochloride in a weight ratio of 1/500 that is allegedly known in the art.

Applicant respectfully reminds the Examiner that there is no such thing as inherent obviousness, since inherency and obviousness are different legal concepts. *See In re Spormann*, 363 F.2d 444 (C.C.P.A. 1966); *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993). That which is inherent cannot be obvious, since inherent information "is not necessarily known . . . . [and] [o]bviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d at 448. For at least these reasons, Applicant respectfully asserts that the Examiner has not established a *prima facie* case of obviousness for the claims.

In sum, based on facts in the record, Applicant asserts that the Examiner has failed to establish a *prima facie* case of obviousness for at least the following reasons: (1) the Examiner has not established that the references teach all the elements of the claims,

particularly a composition comprising glimepiride and metformin hydrochloride, or a composition comprising a synergistic combination of glimepiride and metformin at the specified weight ratios; (2) Seymour teaches away from the use of glimepiride and metformin hydrochloride, and therefore cannot be used to support a *prima facie* case of obviousness of the claims; (3) the Examiner has not provided the requisite rationale to combine the cited references to arrive at the claimed subject matter; and (4) obviousness of the claimed subject matter cannot be predicated on an unknown or allegedly inherent property of the art. Therefore, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Even if prima facie obviousness were established, evidence of unexpected results and commercial success exists that would overcome such a rejection.

Secondary considerations of non-obviousness include unexpected results and evidence of commercial success. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S. Ct. 684, 694, 148 U.S.P.Q. 459, 467 (1966). The Federal Circuit has reaffirmed that the USPTO must in all cases consider any evidence presented by Appellants tending to support secondary considerations of non-obviousness. *In re John B. Sullivan and Findlay E. Russell*, 498 F.3d 1345, 84 U.S.P.Q.2d 1034 (Fed. Cir. 2007). As discussed above, the Examiner has not established a *prima facie* case of obviousness with respect to the claims. Moreover, the record demonstrates that *prima facie* obviousness, even if it were established, would be negated by the unexpected properties and commercially success of the claimed invention, namely, the inventor's discovery of the claimed combination of glimepiride and metformin hydrochloride at a weight ratio of about 1/500.

Here, the Applicant has discovered that compositions comprising a combination of glimepiride and metformin hydrochloride at a weight ratio of about 1/500 have an unexpectedly improved effect on reducing blood glucose levels in diabetic patients. *See, e.g.,* paragraphs [0012], [0014] and [0033] of the substitute specification filed on July 26, 2004 (hereinafter "specification"). As disclosed in the specification, the treatment of patients with compositions comprising a combination of glimepiride and metformin at a weight ratio of 1/500 resulted in unexpected decreases in glycosylated hemoglobin (HbA_{1C}), fasting plasma glucose levels, and prandial blood glucose levels compared to treatments with glimepiride or metformin alone. *See, e.g.,* paragraph [0033] of the specification. These data are reproduced in the table below, along with data from U.S. Patent No. 6,011,049 which measured the same parameters following treatment with metformin and glyburide:

	Metformin 500 mg	**Glimepiride 1 mg**	**Metformin + Glimepiride 500 mg / 1mg**	Metformin + Glyburide 1500 mg / 20 mg (U.S. Pat. No. 6,011,049)
Glycosylated Hemoglobin (HbA_{1c})	+0.06	+0.25	**-0.70**	+0.10
Fasting Plasma Glucose (FPG)	+0.75	+0.68	**-1.77**	+6.0
Prandial Blood Glucose	+1.08	+0.99	**-2.7**	*not determined*

Specifically, the above data show that treatment with compositions comprising glimepiride and metformin, at a 1/500 weight ratio, resulted in a potentiated therapeutic efficacy that is unexpectedly greater than treatment with glimepiride or metformin alone. This potentiated effect was not observed with combined treatment of glyburide and metformin at significantly increased doses (20 times more sulfonylurea and three times

more metformin). Thus, in view of the potentiated therapeutic efficacy observed with compositions comprising glimepiride and metformin at a 1/500 weight ratio, the claimed combinations of glimepiride and metformin would not have been predictable. As such, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that these unexpected results would be sufficient to overcome such a rejection.

Exhibits A and B

As further evidence in support of the non-obviousness of the claimed subject matter, Applicant reminds the Examiner of Exhibit A (González-Oritz *et al.*, *Rev. Inv. Clin.* 56:327-333, 2004; *see* paragraph [0012] of the specification) submitted with the Amendment and Reply Under 37 C.F.R. § 1.116 filed on April 6, 2009. As explained in the Abstract, Exhibit A provides data from a clinical study involving the treatment of diabetic patients with 4 mg of glimepiride alone, 2 g of metformin alone, or 4 mg of glimepiride and 2 g of metformin (1/500 weight ratio) together in the same composition. The efficacy criteria evaluated in the study were either a decrease in glycosylated hemoglobin (HbA_{1C}, or "A1C" in Exhibit A) of 1% or more, or a reduction in A1C of 7% or less. According to the Abstract, the decrease in A1C concentration was -0.9 ± 1.6% in the glimepiride group, -0.7 ± 2.1% in the metformin group, and -1.3 ± 1.8 mg/dL in the combined therapy group. Thus, only the combination therapy group attained the efficacy criteria of decreased A1C of 1% of more. Furthermore, the percentage of patients attaining the efficacy criteria of 1% or more or a reduction in A1C of 7% or less was markedly enhanced in the combination therapy group compared to the monotherapy groups, while the frequency of adverse events was similar for all treatment groups.

Applicant also reminds the Examiner of Exhibit B (González-Oritz *et al.*, *J. Diabetes Complications*) submitted with the Amendment and Reply Under 37 C.F.R. § 1.116 filed on April 6, 2009 as additional evidence in support of non-obviousness. Exhibit B provides data from a clinical study comparing the efficacy of glycemic control in patients treated with 1 mg of glimepiride and 500 mg of metformin (1/500 weight ratio) together in the same composition, to patients treated with 5 mg of glibenclamide (glyburide) and 500 mg of metformin together in the same composition. As detailed in Table 2, the percentage of patients who maintained glycemic control after 12 months of treatment, measured by A1C levels less than 7%, were markedly higher in the glimepiride/metformin treatment groups compared to the glyburide/metformin treatment groups.

In sum, Exhibits A and B provide further support for the non-obviousness of the claimed subject matter because they provide evidence that the claimed combination of glimepiride and metformin unexpectedly met certain therapeutic efficacy criteria compared to monotherapy with glimepiride or metformin alone, or compared to combination therapy with metformin and another sulfonylurea agent. Therefore, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that these unexpected results would be sufficient to overcome such a rejection. For at least these reasons, Applicant respectfully requests this rejection be withdrawn.

Exhibit C

As further evidence in support of the non-obviousness of the claimed subject matter, Applicant reminds the Examiner of Exhibit C submitted with the Amendment

and Reply Under 37 C.F.R. § 1.116 filed on April 6, 2009. Exhibit C provides post-filing date data from a clinical study involving the treatment of patients with type II diabetes with a daily dose of 4 mg of glimepiride alone ("Glimepiride"), 2 g of metformin hydrochloride alone ("Metformin"), or a combination of 4 mg of glimepiride and 2 g of metformin hydrochloride (1/500 weight ratio) together in the same composition ("Glimepiride + Metformin"). Glycosylated hemoglobin (HbA_{1C}) levels were measured prior to treatment ("baseline") and the percent change in HbA_{1C} levels was determined by comparing baseline HbA_{1C} levels to HbA_{1C} levels after treatment. The combination therapy group attained a reduction of HbA_{1C} levels greater than the individual effects of glimepiride or metformin hydrochloride treatment alone. Moreover, only the combination therapy group attained the efficacy criteria of decreased HbA_{1C} of 1% of more.

As such, Exhibit C provides further support for the non-obviousness of the claimed subject matter because it provides evidence of the synergistic effects of the claimed combination of glimepiride and metformin hydrochloride compared to monotherapy with glimepiride or metformin hydrochloride alone. Therefore, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that these unexpected results would be sufficient to overcome such a rejection. For at least these reasons, Applicant respectfully requests this rejection be withdrawn.

Exhibit D

As further evidence in support of the non-obviousness of the claimed subject matter, Applicant reminds the Examiner of Exhibit D (Shimpi, R.D., *et al.*, *Int. J.*

PharmTech Res. 1: 50-61, 2009) provided in Reply Under 37 C.F.R. § 1.111 filed on August 24, 2009. Exhibit D provides data from a clinical study comparing the effects of metformin and glimepiride treatment with metformin and glibenclamide (glyburide) treatment in patients with type 2 diabetes. Specifically, patients were treated with compositions comprising 1000 mg of metformin and 10 mg of glyburide, or with compositions comprising 1000 mg of metformin and 2 mg of glimepiride (1/500 weight ratio). *See, e.g.*, Exhibit D at page 53. After 12 weeks of treatment, reductions in HbA_{1C} levels were observed in both treatment groups; however, patients treated with metformin and glimepiride exhibited significantly reduced HbA_{1C} levels compared to patients treated with metformin and glyburide. *See, e.g.*, Exhibit D at Figure 1. In addition, patients treated with metformin and glimepiride exhibited significantly reduced fasting plasma glucose (FPG) levels compared to patients treated with metformin and glyburide. *See, e.g.*, Exhibit D at Figure 2.

As such, Exhibit D provides further support for the non-obviousness of the claimed subject matter because it provides evidence that the claimed compositions comprising glimepiride and metformin at the specified weight ratios unexpectedly met certain therapeutic efficacy criteria compared to therapy with metformin and glyburide.

Exhibit E

In further support of the non-obviousness of the claimed invention, Applicant provides the attached Declaration Under 37 C.F.R. § 1.132 by Gerardo Gustavo Gómez Bustos ("Declaration") as evidence of the success of commercial products within the scope of the presently claimed pharmaceutical compositions. Gerardo Gustavo Gómez Bustos holds the position of International Business Director at Laboratorios Silanes, S.A.

de C.V. ("Silanes"), the owner of the captioned patent application. Declaration at paragraph 1. His duties include the commercial operation of the company in Central America and the Caribbean, the construction of Strategic Alliances for South America and the negotiation of In & Out License Agreements world-wide. Declaration at paragraph 1. In the Declaration, Gerardo Gustavo Gómez Bustos indicates that Silanes has successfully developed, manufactured and marketed several commercial products having a 1/500 weight ratio of glimepiride/metformin hydrochloride. Declaration at paragraph 2. These products have a significant market presence throughout Mexico, Central America and South America and are the subject of significant licensing and co-marketing agreements between Silanes and third party companies. Declaration at paragraphs 3-8. In addition, these products have been recognized with national awards for innovation, and represent the *first time* a medicine developed in Mexico has been licensed to a transnational company for world-wide sale. Declaration at paragraphs 7-10. It is Gerardo Gustavo Gómez Bustos's opinion that the commercial success of Silanes' commercial products is due to their unique features which were desired by the anti-diabetic market (*i.e.*, a composition comprising glimepiride and metformin together in one tablet, in a synergistic ratio) and were not previously known or available.

Also, after introduction of Silanes' commercial product, the number of prescriptions increased from 2002 through 2007, and sales of Silanes' commercial product remained consistent from 2005 through 2010, with notable increases in sales from 2005 through 2007 and from 2009 through 2010. Declaration at paragraph 11 and Figures 1-2. It is Gerardo Gustavo Gómez Bustos's opinion that these trends in the number of prescriptions and sales were not the result of increased advertising of Silanes'

commercial products. It is also Gerardo Gustavo Gómez Bustos's opinion that the commercial success of Silanes' commercial products is due to their unique features which were desired by the anti-diabetic market (*i.e.*, a composition comprising glimepiride and metformin together in one tablet, in a synergistic ratio) and were not previously known or available.

Therefore, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that this significant evidence of commercial success would be sufficient to overcome such a rejection. For at least these reasons, Applicant respectfully requests this rejection be withdrawn.

At page 12 of the Office Action, the Examiner appears to acknowledge that evidence of non-obviousness is available for the claimed invention, but that the evidence of non-obviousness does not outweigh the evidence of obviousness in view of the teachings in the cited art. Even if such evidence of obviousness were present, Applicant submits that the evidence of non-obviousness previously of record along with the additional evidence of non-obviousness presented herein, is significant enough to establish the non-obviousness of the claimed invention in view of recent USPTO guidance and Federal Circuit case law.

A nexus exists between the evidence of secondary considerations and the claimed invention.

According to MPEP § 716.01(b), any secondary evidence must be related to the claimed invention. To be given substantial weight, evidence of secondary considerations of non-obviousness must be relevant to the subject matter as claimed, and therefore the Examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations. *Ashland Oil, Inc. v. Delta*

Resins & Refractories, Inc., 776 F.2d 281, 305 n.42 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). Because the evidence of unexpected results and commercial success is specifically directed to pharmaceutical compositions comprising a glimepiride/metformin hydrochloride weight ratio of 1/500, a sufficient connection between the objective evidence of non-obviousness and the claimed invention is clearly established. As such, the evidence of nonobviousness of record is of probative value in the determination of non-obviousness of the claimed invention and should be given substantial weight. *See also Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387 (Fed. Cir. 1988), *cert. denied*, 488 U.S. 956 (1988).

The evidence of secondary considerations is commensurate in scope with the claimed invention.

Whether unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support. MPEP § 716.02(d). Because the evidence of unexpected results and commercial success is specifically directed to pharmaceutical compositions comprising a glimepiride/metformin hydrochloride weight ratio of 1/500, it is clearly within and commensurate in the scope of the claimed invention. Thus, this evidence of non-obviousness should be given substantial weight.

2010 KSR Guidelines Update

As mentioned above, the USPTO recently issued "Examination Guidelines Update: Development in the Obviousness Inquiry After *KSR* v. *Teleflex*" to assist USPTO patent examiners with application of the law of obviousness since *KSR* and address evidence of non-obviousness, such as unexpected results and commercial

success evidence. 75 Fed. Reg. 169, pp. 53643-60 (hereinafter "2010 *KSR* Guidelines Update"). In general, the 2010 *KSR* Guidelines Update emphasizes the importance of considering rebuttal evidence of non-obviousness submitted. *Id.* at 53644 and 53657. Once rebuttal evidence has been presented, USPTO personnel should reconsider any initial obviousness determination in view of the entire record and should not summarily dismiss rebuttal evidence as not compelling or insufficient. *Id.* at 53657. In addition, evidence of commercial success is pertinent where a nexus between the success of the product and the claimed invention has been demonstrated. *Id.* at 53658, Example 5.3. Moreover, an obviousness rejection should be made or maintained only if evidence of obviousness outweighs evidence of non-obviousness. *Id.* at 53658, referencing MPEP § 706(I) ("The standard to be applied in all cases is the 'preponderance of the evidence' test. In other words, an examiner should reject a claim if, in view of the prior art and evidence of record, it is more likely than not that the claim is unpatentable."). Based on this guidance, Applicant submits that the significance of the rebuttal evidence of record, the clear nexus between the claimed invention and the rebuttal evidence, and the commensurate scope of the evidence in view of the claimed invention, would outweigh any alleged *prima facie* case of obviousness.

Therefore, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that these unexpected results and commercial would be sufficient to overcome such a rejection. For at least these reasons, Applicant respectfully requests this rejection be withdrawn.

Conclusion

The stated ground of rejection has been properly traversed. Applicant therefore respectfully requests that the Examiner reconsider the presently outstanding rejection and that it be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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Exhibit E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 3497
José Manuel Francisco LARA OCHOA	Art Unit: 1611
Appl. No.: 10/502,403	Examiner: Love, Trevor M.
§ 371(c) Date: June 20, 2005	Atty. Docket: 2099.0090000/PAJ/LMB
For: **Pharmaceutical Composition to Control Blood Glucose in Patients with Type 2 Diabetes**	

Declaration Under 37 C.F.R. § 1.132 by Gerardo Gustavo Gómez Bustos

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Gerardo Gustavo Gómez Bustos, hereby declare and state as follows:

1. I am currently employed at Laboratorios Silanes, S.A. de C.V. I hold the position of International Business Director. My duties include the commercial operation of the company in Central America and the Caribbean, the construction of Strategic Alliances for South America and the negotiation of In & Out License Agreements worldwide. Also I have contributions in the Intellectual Property Strategy of the company. Laboratorios Silanes. A description of my employment history and educational experience is attached as Exhibit E1.

2. Silanes is an independent corporation in México D.F., MÉXICO. Silanes is the assignee of U.S. Patent Appl. No. 10/502,403 ("the '403 application") (recordation at the USPTO to be filed). I am familiar with the subject matter of the '403 application and understand that the present claims are directed to a solid pharmaceutical composition comprising a synergistic combination of glimepiride and metformin hydrochloride, wherein the weight ratio of glimepiride and metformin hydrochloride is about 1/500. As described further below, Silanes has successfully developed, manufactured and marketed commercial products within the scope of pharmaceutical compositions of the claimed invention.

Silanes' Commercial Products Have Significant Market Presence Throughout Mexico, Central American and South America

3. Between 2004 to 2009, Silanes obtained regulatory approval in Central America and South America countries for the treatment of type II diabetes with pharmaceutical compositions containing 2 mg of glimepiride and 1,000 mg of metformin hydrochloride or containing 1 mg of glimepiride and 500 mg of metformin hydrochloride (*i.e.*, a weight ratio of 1/500; hereinafter "Silanes' commercial products" or "Silanes' products"). To date, Silanes has successfully manufactured and marketed the following commercial glimepiride/metformin hydrochloride combination products in the following countries:

COUNTRY	PRODUCT NAME	RELATED AGREEMENTS
Mexico	Glimetal®	Directly commercialized by Silanes
Mexico	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
Guatemala,	Metglital®	Directly commercialized by Silanes
Honduras	Metglital®	Directly commercialized by Silanes
El Salvador	Metglital®	Directly commercialized by Silanes
Dominican Republic	Metglital®	Directly commercialized by Silanes
Guatemala	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
Honduras	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
El Salvador	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
Dominican Republic	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
Brazil	Meritor®	Co-marketed with Aché Laboratories pursuant to a licensing agreement
Ecuador	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
Bolivia	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
Chile	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement

Paraguay	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
Columbia	Glimetal®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
Venezuela	Glimetal®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
Peru	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement
Panama	Amaryl M®	Co-marketed with Sanofi-Aventis pursuant to a licensing agreement

Commercial product information for these products is attached as Exhibit E2. Silanes also manufactures and markets a pharmaceutical composition containing 4 mg of glimepiride and 1,000 mg of metformin hydrochloride.

4. Therefore, Silanes has successfully obtained approval for and has manufactured and marketed several commercial products within the scope of the '403 application claims throughout Mexico, Central America and South America.

Sanofi-Aventis and Aché Laboratories have licensed and jointly commercialize Silanes' commercial products with Silanes throughout Mexico, Central America and South America.

5. In 2007, Sanofi-Aventis and Silanes signed an agreement to jointly commercialize the Silanes' products in Mexico, Central America and South America. *See* Exhibit E3 which provides a published article from *El Financiero* dated November 27, 2008, along with its English translation; Exhibit E4 which provides a published article from *Crónica* dated November 26, 2008, along with its English translation; and Exhibit E5 which provides a published article from *Mural* dated November 26, 2008, along with its English translation. This agreement permitted Silanes to increase its production by 42%, or up to 850 million tablets. *See* Exhibit E3.

6. In 2006, Silanes also signed an agreement to develop and commercialize Silanes' products in Brazil with Aché Laboratories. *See* Exhibit E6 which provides a published article from *Excélsior* dated November 26, 2008, along with its English translation.

7. In the United States, it is not uncommon for small laboratories or universities to develop new pharmaceutical agents and to jointly develop and commercialize them with larger pharmaceutical companies. However, in Mexico, this is not common practice. In fact, Silanes' commercial products represent ***the first time*** a medicine developed in Mexico has been licensed to a transnational company for world-wide sale. *See* Exhibit E7 which provides a published article from *El Norte* dated November 25, 2008, along with its English translation.

8. It is my opinion that one reason for Silanes' ability to have licensed and jointly commercialized its products to other companies, for the first time in Mexico, is that these companies appreciate and value the significance of the claimed invention described in the '403 application and desire to secure agreements to license, develop and market products that embodiment the claimed invention.

Silanes was been awarded other accolades for the innovation of the commercial products

9. Silanes was awarded the Canifarma (Mexican National Chamber of the Pharmaceutical Society) Award for Technological Research and Development in 2008 and the Mexican Association of Directors of Applied Research and Technological Development (ADIAT) Prize for Technological Innovation in 2009 for the commercial products. *See* Exhibit E8 which provides an English translation of a published article from *Negocios* (accessed on-line on September 19, 2010).

10. It is my opinion that one reason that Silanes and Silanes' commercial products have received such recognition is that these organizations value the significance of the commercial products that embody the claimed invention of the '403 application.

Prescription Numbers and Sales of Silanes' Commercial Products Increased When Introduced to the Market

11. Sales of Silanes' commercial products began in México in 2002. After introduction of the products, the number of prescriptions increased from 2002 through 2007 as evidenced by Figures 1 and 2 below. Additionally, sales of Silanes' commercial products

remained consistent from 2005 through 2010, with notable increases in sales from 2005 to 2007 and then from 2009 through 2010 with the co-market with Sanofi-Aventis.

Product	G/M Amounts	July/2006		July/2007		July/2008		July/2009		July/2010	
		Px	%	Px	%	Px	%	Px	%	Px	%
GLIMETAL		**4,730**	**5.36**	**8,012**	**4.33**	**7,852**	**4.02**	**7,034**	**3.47**	**4,434**	**2.43**
GLIMETAL	4MG/1GR	2,139	2.43	3,650	1.97	3,770	1.93	3,421	1.69	2,172	1.19
GLIMETAL	2MG/1GR	1,801	2.04	3,056	1.65	2,868	1.47	2,550	1.26	1,529	0.84
GLIMETAL	500/1MG	790	0.9	1,306	0.71	1,214	0.62	1,063	0.52	733	0.4
AMARYL M		**0**	**0**	**0**	**0**	**0**	**0**	**2,199**	**1.08**	**4,103**	**2.25**
AMARYL M	4MG/1GR	0	0	0	0	0	0	1,266	0.62	2,386	1.31
AMARYL M	2MG/1GR	0	0	0	0	0	0	933	0.46	1,700	0.93
AMARYL M	2/500MG	0	0	0	0	0	0	0	0	17	0.01

Figure 1: Prescription & % of Market Share Data For Silanes' Commercial Product in Mexico
G/M Amounts: Amount of Glimepiride/ Amount of Metformin
Px: Prescription
%: % of Market share

Product	G/M Amounts	Dec/2002	Dec/2003	Dec/2004	Dec/2005	Dec/2006	Dec/2007	Dec/2008	Dec/2009	Accumulated /2010 Ago
AMARYL M						**0**	**0**	**469,825**	**3,771,623**	**5,364,076**
AMARYL M	**2 MG /1 GR**					0	0	186,884	1,269,769	1,398,650
AMARYL M	**4 MG /1 GR**					0	0	282,941	2,501,854	3,965,426
GLIMETAL		**1,399,310**	**5,250,257**	**9,344,695**	**14,172,407**	**15,890,270**	**15,419,352**	**15,974,832**	**13,098,979**	**8,596,411**
GLIMETAL	2MG/1000 MG	478,239	1,730,894	3,111,529	4,856,930	5,395,882	5,072,383	5,197,862	4,306,835	2,737,825
GLIMETAL	4MG /1000 MG	703,893	2,720,049	5,003,976	7,541,345	8,508,959	8,504,653	9,077,284	7,339,808	4,892,600
GLIMETAL	1MG /500 MG	217,178	231,241	793	73	447	606	523	255	0
GLIMETAL	1MG /500 MG	0	568,073	1,228,397	1,774,059	1,984,982	1,841,710	1,699,163	1,452,082	965,987

Figure 2: Sales Data in USD For Silanes' Commercial Product in Mexico
G/M Amounts: Amount of Glimepiride/ Amount of Metformin

The data for Figures 1 and 2 were obtained from internal records of Silanes and the real number values have been rounded.

12. By virtue of my position at Silanes, I have knowledge of the marketing and advertising expenditures made in relation to Silanes' commercial products. It is my opinion that the above mentioned trends in the number of prescriptions and sales were not the result of increased advertising of Silanes' commercial products.

13. It is also my opinion that, from a consumer product point of view, the commercial success of Silanes' commercial products is due to their unique features which were desired by the anti-diabetic market (*i.e.*, a composition comprising glimepiride and metformin together in one tablet, in a synergistic ratio) and were not previously known or available.

14. In signing below, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of U.S. Patent No. 5,550,156 or any certificate resulting therefrom.

Gerardo Gustavo Gómez Bustos

September 22nd, 2010.
Date

1260237

Exhibit E1

GERARDO GUSTAVO GOMEZ BUSTOS

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Educational:

Bachelor Degree in Economics by the National Autonomous University of Mexico (1977)

Employment History:

2004 – Current: Laboratorios Silanes, S.A. de C.V., as International Business Director.

2001-2004: Independent Consultant in Foreign Investment, Technology Transfer Agreements and Industrial Property Rights.

1995-2001: National Bank of Rural Credit, as Manager of Credit for the states of Puebla, Morelos, Tlaxcala and Hidalgo.

1991-1995: Mexican Coffee Institute and Mexican Coffee Council, as Director of Operations

1989 – 1991: Ambito Empresarial, A.C., as Founder and Partner. Consulting Firm in Foreign Investment, Technology Transfer, Patents and Trademarks.

1979 – 1988: Ministry of Commerce and Industry, as Director of Evaluation of Technology Transfer Agreements and Patents and Trademarks Licenses.

Current Activities:

Responsible of the commercial operations of the company in Central America and the Caribbean.

Construction of Strategic Alliances in South America

Negotiation of In & Out License Agreements worldwide.

President of the Industrial Property Committee in the National Association of Medicines Manufacturers in Mexico.

President of the Industrial Property Commission in the National Chamber of the Pharmaceutical Industry in Mexico.

Exhibit E2

GLIMETAL*

TABLETS

Treatment of the diabetes mellitus

H.P. LABORATORIOS SILANES, S.A.

GENERIC DENOMINATION:

Glimepirida and metformina.

IT FORMS PHAMACIST AND FORMULATION:

Each tablet contains:

Glimepirida	1 mg	2 mgs	4 mgs
Hydrochlorate of metformina	500 mgs	1.000 mgs	1.000 mgs
Excipiente, cbp	1 tablet	1 tablet	1 tablet

THERAPEUTIC INDICATIONS:

Indicated GLIMETAL* this for the treatment of diabetic associated type 2 to the changes of life style:

- Diabetic Type 2 of just diagnosis with resistance to suitably follow the changes of life style.
- Diabetic Type 2, obese, with overweight or normal weight, failure to the dietetic regime and without tendency to the cetosis.
- Diabetic Type 2, under therapy with diet and fails to sulfonilureas with tendency to the increase of weight.

- Diabetic obese Type 2, with overweight or normal weight, diet and sulfonilureas, secondary upheaval of lipids to the diabetes.
- Diabetic Type 2 under dietetic regime and with secondary fault to the biguanidas sulfonilureas or.
- Diabetic Type 1 (insulino employee) under dietetic regime and insulin, to reduce the dose of this last one, never to replace it.

PHARMACOKINETIC AND FARMACODINAMIA IN HUMANS:

Glimepirida completely is absorbed of tract GI obtaining itself bioavailability of 100% and being significant from the first hour. The metformina is absorbed partially in a lapse of 1 to 3 hours, with bioavailability from 50 to 60%. The coadministration of both drugs with foods does not produce important kinetic effects that they are reflected in the clinic.

With glimepirida, obtained Cmax , 232 average of 352 ± 222 ng/ml and 591 ± ng/ml with a single dose of 4 or 8 mgs respectively in a Tmax , of 2,5 hours. For multiple dose, administered during 10 days, numbers of Cmax , 309 were reported ± 134 ng/ml (with 4 265 mgs) and 578 ± ng/ml (with 8 mgs) in a Tmax , of 2,8 hours. With the metformina the area under the curved concentration-time (ABC) reached was of 10,83 mcg/ml/hr. After the unique oral administration of 1 g of metformina to diabetics type 2, the maximum 3,25 plasmatic levels went mcg/ml and less than lowered to 0,1 mcg/ml to the 24 hours post administration.

The glimepirida one leagues together to plasmatic proteins in 99.5%, whereas the metformina does in almost null form and a part of her is distributed in erythrocytes.

The glimepirida one extensively is metabolizada by the liver having produced 2 metabolites. The cytochrome C450 II C9 is involved with the formation of the derivative cyclohexyl-hidroximetil (active) and this one later is biotransformado by cytosolic enzymes towards metabolite carboxi (inactive). The metformina however not biotransforma.

Glimepirida 63% of excrete by renal route (almost everything like metabolites) and the rest with the bile (also almost in its totality like metabolites). The metformina is eliminated in inalterable form in 90% by renal route (tubular secretion), probably a small amount is eliminated by saliva.

The average life (t ½) of elimination of the glimepirida one is of 5 to 9 hours and the one of its metabolites cicloexil hidroximetil of 3 hours and carboxil metabolite of 5 hours. The t ½ of plasma elimination of the metformina to simple dose is of 1,5 to 6,2 hours, and to multiple dose it was increased to 19,8 hours. On the other hand the t ½ of elimination in blood is of 17,6 hours, which suggests metformina is distributed by erythrocytes.

The metformina is removed in effective form by hemodiálisis (to see Sobredosificación).

The fixed combination of these two medecines in GLIMETAL* provides by different mechanisms of action, the following favorable effects:

It increases the number of receivers to the insulin, that causes a recovery in the connection capacity "receiving insulin", which leads to a reduction of hiperinsulinemia and the resistance to the insulin.

By action of the glimepirida one β to the stimulus of the glucose is increased to sensitivity of the cells, favoring in this way the endogenous insulin synthesis and secretion. The metformina not to act in páncreas does not increase the level of insulin, diminishes the gluconeogénesis and the production of hepatic glucose at the same time as it causes one better use of the

glucose at peripheral level.
The glimepirida one modifies the plaquetaria aggregation via the suppression of the metabolism of araquidónico acid (it is an inhibitor of ciclooxigenasa, but not of lipooxigenasa). Like the tromboxano A2, an endogenous activator of plaquetas is product of this route, the glimepirida one owns the benefit Annex in the diabetes mellitus, when reducing the microvascular complications related to hypersensitivity and increase of the function of plaquetas.
The glimepirida one closes the potassium channels (K+) employees of ATP of the cells β via a protein union. The despolariza membrane and provides the signal to the calcium channels (Ca2+) voltage dependent so that they abran and they allow the entrance of the calcium ion flow.
The increase in the intracellular calcium concentration shoots the insulin secretion.
On the other hand, the increase of calcium in citosol activates a second type of potassium channel, dependent the calcium potassium channel (Ca2+) which abre and causes repolarización; this favors the closing of the calcium channels, so that the cycle is reinitiated.
Although the mechanism of metformina action totally is not clarified, increases the tie of insulin to its receivers and potentialises the action of her at cellular level. The consistent and direct effect of metformina in the glucose transport is reinforced concerning the skeletal muscle, when increasing the intracellular transport of the glucose. As the skeletal muscles are qualitatively the most important most sensible glucose users and of peripheral weaves to the insulin, the authors suggest the hipoglucémico effect of the metformina this half-full one via the increase of the use of the glucose by skeletal muscles.
With the administration of glimepirida per prolonged periods maintained reductions of the peripheral glucose are obtained, which is translated in an improvement in the function of the pancreatic cells β and the use of the glucose by the fatty weave, hepatic and muscular, that is reinforced by the action of the metformina especially concerning the muscular weave through the anaerobic route by inhibition of oxidating enzymes.
The high cholesterol levels, triglycerides and lipoproteins of low densidad (LDL), secondary to the metabolic upheaval, are reduced by action of the metformina, which also increases the activity fibrinolítica and diminishes the plaquetaria adhesiveness; these effects help to reduce the risks of so frequent cardiovascular complications of observing in the diabetic patients.
The metformina, diminishes the absorption of glucose at intestinal level at the same time as it stimulates the center of the satiety, which leads to the diminution of the corporal weight of the diabetic patient with overweight and aid to maintain the weight of the diabetic normopeso. Combined to these actions it reduces hipertrigliceridemia diminishing the factor of risk of the aterosclerosis.

CONTRAINDICATIONS:

Hypersensitivity to the metformina glimepirida one and/or, as well as to other biguanidas sulfonilureas or. Diabetic Cetosis. Hipoglucémicos states. Hepatic and/or renal insufficiency severe. Ingestion of spirits. Diabetes type I like insulin substitute. Operations. All those pathologies that attend or bring about a hypermetabolic state of hypoxia or states like: age cardiovascular outpost, alterations, cardiorrespiratorias, serious infections (bacteremias,

septicemias, neumopatías), traumas, fever, dehydration and adrenal insufficiency or pregnancy.
Radiological studies that use means of resistance IV recommend to suspend to the administration of the medicine 48 hours before carrying out the radiological study and resuming their administration 48 hours after it to have finished, in order to prevent a lactoacidosis.

GENERAL PRECAUTIONS:

To conserve the attachment to diet, exercise and ingestion of the medicine they are fundamental to guarantee the effectiveness of GLIMETAL* in the control of the diabetes, as well as to avoid pictures of hipoglicemia.
The metformina is the biguanida one with lower inductive index of lactoacidosis, (0,24 by each 10.000 patients) and can be avoided if the maximum permissible dose per day and its contraindications is had in mind. Before the presence of this picture one will be due to suspend his administration and to apply the corrective therapeutic measures.
Obese, elderly or that attends with renal insufficiency, hepatic or hipofisiaria patients, must very be watched close by avoiding appears a hypoglucaemia.
In case of planned surgery, to suspend to the GLIMETAL* administration the day of the surgery and to restore insulínica therapy, when the patient can to return to use the buccal route and postsurgical contraindication does not exist, will be reinitiated the GLIMETAL* administration fitting the dose to the metabolic conditions and the dietetic plan.
Patients with sensible or inflamed gastroduodenal mucosa, to initiate the therapy with low dose and to be increasing it each 2 to 3 weeks, always administering the medicine with foods or immediately after them.
To monitor levels annually B12 the vitamin (9% of cases dealt with metformina present/display diminution of their values).

RESTRICTIONS OF USE DURING THE PREGNANCY AND THE LACTANCIA:

The GLIMETAL* use is contraindicated during the pregnancy and the lactancia.

SECONDARY REACTIONS AND ADVERSE:

GLIMETAL* is a tolerated medicine or, the secondary reactions have direct relation with the dose, they are transitory and they respond to the reduction of the dose or to the suspension of the medicine. Nevertheless there are reports of which as with other oral hipoglucemiantes, some indirect effect due to hypersensitivity can be severe.
Gastrointestinal reactions: They are most frequent to observe in the clinic and are nausea, vomit, sensation of fullness, pirosis, anorexy, diarrhoea and bitter or metallic flavor, that often correct when dividing the daily dose in two takings.
In rare occasions colestática jaundice can happen, in this case will be due to suspend GLIMETAL*.
Metabolic reactions: Hipoglucemia and lactoacidosis. Selecting to the patient, as well as having presents the contraindications, precautions and the maximum permissible dose in 24 hours, will avoid the outbreak of these effects collaterals.
The lactic acidosis by metformina is not generally induced when avoiding preexisting factors of risk (renal insufficiency, hepatic disease, alcoholism, intercurrente infection or cardiopulmonary

insufficiency) that condition impediment of suitable perfusión of weaves or reduced lactate elimination.
Dermatológicas reactions: Prurito, erythema, urticaria and injuries maculopapulares. All of them are generally transitory and of little magnitude, that frequently disappears during the therapy with GLIMETAL*. In sporadic cases one becomes necessary to suspend the medicine.
Hematological reactions: Most frequent they are diminution of the plaquetaria aggregation and increase of the time of coagulation, which in patients with cardiocirculatorios upheavals are to be desired to help to diminish the cardiovascular risks.
Sporadic reports of leukopenia, agranulocitosis, trombocitopenia, haemolytic anemia, aplástica anemia and pancitopenia, essentially by its sulfonilureico component.
Reduction of absorption has been reported sporadically B12 the vitamin in diabetics dealt with metformina by lapses majors of 2 years, the one that can cause megaloblástica anemia. For this reason, it is recommended in the patients who are treated per prolonged periods, determination sérica B12 vitamin and haematic biometry.
Cardiac reactions: The insulin and the sulfonilureas can cause hypoglucaemia, to cause catecholamine liberation, which can as well trigger crisis of angor and arrhythmias.
MEDICINAL INTERACTIONS AND OF ANOTHER ONE I GENERATE:
The medicinal interactions that appear with GLIMETAL*, are not exclusive of this combination, since they are shared by other biguanidas sulfonilureas and.
Medecines that potentialise the hipoglucemiante action: Tiótico acid, antiinflammatories nonesteroideos, β blocking adrenérgicos, biguanidas, bezafibrato, clofibrato, chloramphenicol, ciclofosfamida, anabolizantes steroids, fenfluramina, fosfamida, fluconazol, fenilbutazona, fluoroquinolonas, gemfibrozil, insulin, inhibitors of the MAO, itraconazol, inhibitors of the ECA, miconazol, parenteral pentoxifilina (high doses), probenecid, hipoglucemiantes sulfonilureas, sulfametoxazol, sulfatiazol, sulfisoxazol, sulfadiacina, sulfonamide, sulfinpirazona, salicylates and tetraciclinas.
Medecines that diminish the hipoglucemiante action: Nicotínico acid (high doses), acetazolamida, inhibiting of channels of calcium, barbiturates, corticoids, clonidina, estrogens, fenotiazina and derivatives, glucagón, tiroideas gestágenos, hormones, isoniacida, laxatives (high doses), rifampicina, simpaticomiméticos, tiazidas and other saluréticos.
Other medicinal interactions: The catiónicos drugs compete with metformina by the tubular renal secretion (cimetidine, ranitidina, amilorida, digoxina, morphine, quinine, quinidina, triamtereno, trimetoprim and vancomicina) increasing the concentration of metformina.
The inhibitors of the histaminic receivers H2, can potentialise or diminish the hipoglucemiante effect.
The ingestion of spirits with sulfonilureicos or biguanídicos medecines can bring about a disulfirámica reaction, independent of the fact that they can potentialise or diminish the hipoglucémico effect of them.
The effect of the anticoagulants and the fibrinolíticos are potentialised by the metformina.
Nutritional interactions: The foods do not alter the absorption of GLIMETAL* thus can be administered before, with or after ingesting foods, by the pharmacological characteristics of GLIMETAL* it is advised to immediately administer it with foods or after ingesting them.

ALTERATIONS IN THE RESULTS OF LABORATORY TESTS:
The sulfonilureas as the glimepirida one at the beginning of the therapy can elevate in transitory form the creatinine, fosfatasa alkaline, the SGOT and the SGPT.
The metformina lifts the time of coagulation and diminishes the plaquetaria aggregation.
PRECAUTIONS IN RELATION TO CARCINOGENESIS EFFECTS, MUTAGENESIS, TERATOGENESIS AND ON THE FERTILITY:
Realised studies, directed to the search of alterations in animal, did not show to effects nor alterations in these headings.
DOSE AND VIA OF ADMINISTRATION:
Via of administration: Oral.
The monitoring of the answer through the determination of glucosilada hemoglobina is recommendable (HbA1c), since this one is better indicator of the long term glucémico control that the glucaemia in uninformed or after-lunch, also, must be noticed to the patient one on the conduct to follow in case of forgetfulness of one of the doses (never to solve that forgetfulness increasing the dose in the following taking), as well as before the omission of some of its meals or changes in the amount of exercise that is used to realising.
GLIMETAL* does not replace the change of life style, therefore, this one must always accompany the administration by the medicine.
GLIMETAL* is not a substitute of the insulin, but it can be associated to her to diminish daily doses and/or their applications, always combined to a complete plan of change of life style.
The dose suggested for beginning of treatment with GLIMETAL* in Diabetic type 2 (noninsulino employee) is with the lowest dose (1 500 glimepirida mg and mg of metformina) and to realise gradual adjustments to determine the effective minimum dose with which the control of the glucaemia in each patient is obtained.
GLIMETAL* preferably will have to be administered with the breakfast or the first main ingestion of the day. to require 2 either the more tablets to the day it will be distributed in two or three takings with foods.
In order to establish the dose of maintenance, the adjustments of increases or diminutions of the dose are realised every 15 days and will be based on the test resultses of laboratory and the tolerance. Once obtained the metabolic control the effectiveness must be evaluated with measurements of the glucosilada hemoglobina (HbA1c) every 3 months.
The use of sulfonilurea with insulin allows a reduction of up to 30% in the dose of daily insulin necessary to reach glicemia wished.
The association of metformina and insulin allows the best use of this last one with the consequent reduction of the dose until in 25%, for that reason in the combined therapy sulfonilurea and metformina insulin, the insulin requirements will be lower than when this one with anyone of drugs is combined separately and it is recommended to initiate with lower doses of insulin (less 4 U).
Diabetic type 2 with renal insufficiency: To reduce in 50% the normal daily dose of GLIMETAL* and in the same proportion will become the increase or diminution every 15 days, previous determination of glucaemia and valuation of the renal operation.
Hepatic insufficiency: Since the glimepirida one is extensively metabolizada in the liver, it is

suggested in patients with slight insufficiency, to initiate to the dose of ½ tablet to the day and to be increasing carefully under a strict glicémico control. In patients with severe insufficiency to avoid its use.

Geriatrics: It does not seem to have necessity of a particular conduct in these patients, exception done of which presents/displays alterations condition that them to hypoxia states since the metformina does not respond to these alterations well being able to favor the lactoacidosis presence.

Substitution of another oral antidiabetics: If the patient is being controlled with a sulfonilurea that is not the cloropropamida one, to suspend it 24 hours and to initiate the therapy with GLIMETAL*; if she is cloropropamida to suspend it and to wait for 48 hours before administering GLIMETAL*.

The maximum permissible dose per day is:

Concentrations	Maximum permissible dose to the day
1 mg glimepirida with 500 mgs of metformina	6 tablets
2 mgs glimepirida with 1.000 mgs of metformina	3 tablets
4 mgs glimepirida with 1.000 mgs of metformina	1 ½ to 2 tablets

MANIFESTATIONS AND HANDLING OF THE SOBREDOSAGE OR ACCIDENTAL INGESTION:

The sobredosage in diabetic patients, causes hypoglucaemia and/or lactic acidosis. The accidental ingestion by nondiabetic person, following the dose can produce hypoglucaemia of variable intensity that goes in direct proportion to the ingested dose.

The hypoglucaemia is characterized by hunger, anxiety, profuse perspiration, tremors, irritability, restlessness, confusional state, vertigo, palpitations, pallor, parestesias, and hiperestesias of lips, nose, fingers, nauseas, vomit, neurological convulsions and other alterations being able to arrive until the coma. To confirm the hypoglucaemia by the habitual methods of laboratory or with reactive strips.

In slight cases of hypoglucaemia (there is no loss of brings back to consciousness nor neurological symptoms), to administer by mouth, if there are vomit, foods or no rich drinks in glucose.

In moderate or serious cases to administer by fast endovenosa route a glucosada solution to 50%, followed of glucose solution 5 or 10% in continuous infusion, at a speed that maintains the sanguineous glucose level in 100 mg/ml.

Narrow monitoring is required during 48 hours after to have standardized the sanguineous levels to avoid relapses.

Lactic acidosis or lactoacidosis: The picture is characterized by nausea, vomit, abdominal malaise, sensation of fullness, pirosis, anorexy, mialgias, lactoacidemia by above of 5 mmol/lt., and elevation of sérica creatinine; in such case of suspending the medicine to restore symptomatic intensive therapy and narrow monitoring. The hemodiálisis removes the metformina indeed and can correct the lactic acidosis induced by metformina.

The frank clinical picture presents/displays the warning symptoms and signs and in addition hyperventilation, hypothermia, cardiovascular collapse, comma, diminution of the sanguineous

pH (7,2 either the less), lactacidemia of 5 mmol/lt., or major, creatinemia, and elevation of the relation piruvato lactate/.
Before such picture to hospitalize the patient, to suspend the medicine, to restore intensive therapy to correct the acidosis and if the equipment necessary is had to dializar to the patient.

PRESENTATIONS:

Box with 16 tablets grooved with 1 glimepirida mg of and 500 mgs of metformina.
Box with 32 tablets grooved with 1 glimepirida mg of and 500 mgs of metformina.
Box with 16, 20 or 40 tablets grooved with 2 glimepirida mgs of and 1000 mgs of metformina.
Box with 16 tablets grooved with 4 glimepirida mgs of and 1000 mgs of metformina.

RECOMMENDATIONS ON STORAGE:

Consérvese to room temperature to not more of 30°C and in dry place.

PROTECTION LEGEND:

It is not used in the pregnancy nor in the lactancia. Exclusive Literature for doctors. It is not left within reach of the children. Its sale requires medical prescription.

LABORATORY AND DIRECTION:

H.P. LABORATORIOS SILANES, S.A.
Axis 3 North. Núm. 200 Esq. Prolongation 6 North
Industrial park Toluca 2000
52,8 km Toluca-Naucalpan Highway
50200 Toluca, Edo. of Mexico
* Registered mark

I NUMBER OF REGISTRY AND KEY IPPA:

Reg. Núm. 241M2001, SSA IV
083501415E0023/IPPA

Exhibit E3

MONITOREO MEDIOS IMPRESOS

LABORATORIOS SILANES

Medio	Autor	Palabras clave	Fecha
El Financiero	Leticia Hernández	Laboratorios Silanes, glimepirida, metformina	27-noviembre-08

Negocios negocios...

Leticia Hernández M.

Silanes

Comercialización conjunta de antidiabético

Laboratorios Silanes y Sanofi-Aventis acordaron la comercialización conjunta en México y el extranjero de una combinación innovadora para el tratamiento de la diabetes mellitus tipo 2 (DMT2), acuerdo que permitirá a la empresa mexicana elevar su producción de medicamentos para diabetes en 42 por ciento el próximo año, equivalente a 850 millones de tabletas.

Al desarrollar y patentar los principios activos de la *glimepirida* y la *metformina*, que dotan de mayor efectividad al tratamiento de la enfermedad al administrarse en una sola toma al día y permitir el cumplimiento adecuado del tratamiento por el paciente, Laboratorios Silanes se apoyará del posicionamiento y la fuerza de ventas de Sanofi-Aventis en Latinoamérica para su venta, región en donde la enfermedad cobra 100 mil vidas cada año.

Además, con la licencia compartida cada laboratorio podrá comercializarlo en México bajo sus respectivas marcas.

Con una inversión equivalente al 10 por ciento de sus ventas para investigación y desarrollo de productos, Silanes se ha posicionado en el país con sus antidiabéticos orales con los que se tratan diariamente cerca de 600 mil personas.

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Monitored printed media

Laboratorios Silanes

Source	Author	Key words	Date
El financiero	Leticia Hernandez	Laboratorios Silanes, glimepiride, metformin	November 27, 2008

JOINT COMMERCIALIZATION OF AN ANTIDIABETIC

Laboratorios Silanes and Sanofi-Aventis came to an agreement for shared commercialization in Mexico and abroad for an innovative composition for the treatment of Diabetes Mellitus type 2 (DMT2), this agreement will permit to the Mexican company to increase their medicament production for diabetes in 42% the next year, equivalent to 850 millions of tablets.

Developing and patenting the active principles of glimepiride and metformin, which proportionate increased effectiveness to the treatment of the disease taking in a single dose a day and allowing patient's adherence to treatment, Laboratorios Silanes will be supported, by Sanofi-Aventis in Latin-America due to their commercial prestige and their sales force management system, in this geographical zone, this disease takes about 100 thousand lives a year.

Moreover, with the shared license, each laboratory could commercialize in Mexico using their respective brands. With an investing of 10% of sales for Research and development of products, Silanes has placed in a good position in the country with its oral anti-diabetics which are used to treat around 600 thousand people.

Exhibit E4

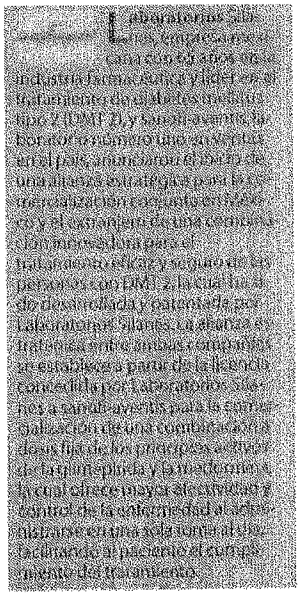
CEFoRP

Comunicación Especializada en Farma & Relaciones Públicas

MONITOREO MEDIOS IMPRESOS

LABORATORIOS SILANES

Medio	Autor	Palabras clave	Fecha
Crónica	Redacción	Laboratorios Silanes, glimepirida, metformina	26-noviembre-08



CEF&RP

Communication Specialized in Pharma & Public Relations

Follow up of printed media

Laboratorios Silanes

Means	Author	Words	Date
Chronicle	Redaction	Silanes Laboratories, glimepiride and metformin	26-November-08

Laboratorios Silanes , a Mexican company with 65 years in the pharmaceutical industry and leader in the diabetes mellitus type 2 (DMT 2) treatment, and the Sanofi-Aventis laboratory, the number one in sales in the country, announced the beginning of a strategic alliance for the joint commercialization in Mexico and abroad of an innovating combination, for the effective and safe treatment of patients with DMT 2 diabetes, that has been developed and patented by Silanes Laboratories. This strategic alliance between the companies was formed because of the licensing by Silanes Laboratories to Sanofi-Aventis for the commercialization of a fixed dose combination of the active principles of glimepiride and metformin, which offers major effectiveness and control of the disease when administered in a single taking a day facilitating the fulfillment of the treatment to the patient.

Exhibit E5

MONITOREO MEDIOS IMPRESOS

LABORATORIOS SILANES

Medio	Autor	Palabras clave	Fecha
Mural	Sara Cantera	Laboratorios Silanes, Glimetal	26-noviembre-08

Concreta alianza Silanes con laboratorio francés

México.- El laboratorio mexicano Silanes y el laboratorio francés Sanofi Aventis anunciaron una alianza estratégica para comercializar Glimetal, un medicamento para el tratamiento de la diabetes tipo dos, en Colombia, Venezuela y otros países latinoamericanos.

El fármaco fue desarrollado y patentado por Silanes, pero se comercializará en América Latina por Sanofi Aventis bajo la marca Amryl.

Sara Cantera

CEF&RP

Communication Specialized in Pharma & Public Relations

Follow up of printed media

Laboratorios Silanes

Source	Author	Words	Date
Mural	Sara Cantera	Laboratorios Silanes, Glimetal	November 26-08

SETTING ALLIANCE SILANES AND FRENCH LABORATORY

Mexico. The Mexican laboratory Silanes and the French laboratory Sanofi Aventis announced an strategic alliance to commercialize Glimetal, a medicament to treat type 2 diabetes, in Colombia, Venezuela and other latin-american countries.

The medicine was developed and patented by Silanes, but will be commercialized in Latin-america by Sanofi Aventis with the brand Amaryl.

Exhibit E6

MONITOREO MEDIOS IMPRESOS

LABORATORIOS SILANES

Medio	Autor	Palabras clave	Fecha
Excélsior	Marielena Vega	Laboratorios Silanes	26-noviembre-08

Silanes, más que una alianza

Hace unos días Laboratorios Silanes firmó una alianza con Sanofi Aventis, sin embargo, le pedimos comentar que esta firma mexicana ya gestiona una más con un laboratorio español en pro de alcanzar una presencia en más de 60 países a nivel mundial y duplicar su tamaño.

La directiva de la empresa nos lanza con más de 60 años de gestión de acuerdos productivos, principalmente para ir por la conquista de los mercados europeo y estadounidense, aunque los latinos también son de su interés.

De ahí que **Antonio Silanes** y su equipo ya gestionan con un laboratorio madrileño con el objetivo de comenzar un acuerdo estratégico para el desarrollo de nuevas formulas dirigidas a atender enfermedades degenerativas, principalmente la diabetes, y problemas cardiovasculares.

A fin de cuentas, este acuerdo junto con el recientemente de Aventis y Aclon, que encuentra **José Méndez Silva**, van haciendo a Laboratorios Silanes una firma mexicana de talla internacional.

Entre los planes de esta compañía se encuentra el que en un lapso de tres años el valor de su mercado de exportación no sólo represente 10% sino 50 por ciento.

De tal forma que Silanes equilibre sus fuentes y continúe a competir en las grandes ligas.

Aunque es una realidad que tendrá que hacerlo con algunos de sus medicamentos más fuertes, difícilmente sus más de 80 medicinas saldrán de territorio azteca, dado que los costos para posicionar a todas serían altísimos, de lo que está muy consciente la directiva de este laboratorio mexicano.

Como también está al tanto del desarrollo de la investigación en moléculas para combatir la diabetes; si no fuera así, simplemente Silanes no proyectaría incrementar 42% su producción de tratamientos para la diabetes el próximo año, que equivaldría a 8.6 millones de tabletas.

Y qué decir de los beneficios que ya recibe vía el Tratado de Libre Comercio de América del Norte, que le permitió entrar al mercado estadounidense y mexicano para combatir enfermedades cardiovasculares y la diabetes.

El mercado de antidiabéticos orales es valuado en más de 145 millones de dólares con un desplazamiento anual de 20 millones de unidades en el sector privado.

Además de combatir un mercado lucrativo farmacéutico que desplaza unos mil 400 millones de unidades al año, 40% más del mercado nacional.

En fin, la realidad es que Silanes da los pasos que ningún otro laboratorio mexicano ha podido dar en el marco de la tecnología, donde avances tan importantes como la biotecnología y la investigación desde hace varios años atrás son parte de su razón de ser.

Así que habrá que seguirle la pista a este laboratorio mexicano que va de frente y con todo a combatir esta crisis que, si bien es cierto afectará el rumbo de muchas empresas, también es una oportunidad para que otras compañías, y parece que Laboratorios Silanes será una de ellas y seguirá abriéndose brecha.

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Follow up of printed media

Laboratorios Silanes

Source	Author	Key Words	Date
Excélsior	Marielena Vega	Laboratorios Silanes	November 26-08

SILANES, MORE THAN AN ALLIANCE

Some days before, Laboratorios Silanes signed an alliance with Sanofi-Aventis, however, we can comment that this Mexican firm has already negotiate agreements with one more with an Spanish pharmaceutical in favor on reach a presence in more than 40 countries all over the world and duplicate its size.

The principle of the mexican company with more than 65 years old, is negotiate with a laboratory from Madrid, with the objective of initiate an strategic agreement to develop new formulas directed to attend degenerative diseases, mainly diabetes, and cardiovascular troubles.

At the end, this agreement together with the recent between Aventis and Aché, directed by José Mendez Silva, are becoming Labotarios Silanes to be an international mexican firm.

Among the plans of this company, is that, at the end of 3 years, its exportation sales represents not only 10% but 50%.

In this way, Silanes could equilibrate its finances and start to compete in major leagues. It is real that must to be done with some of it more strong medicines, hardly its more than 80 medicines will go out from Aztec lands, due to the cost to send all of

them, would be extremely high, the directive of this Mexican laboratory is conscious of this.

It is also up to date regarding the development of research in molecules to fight diabetes; if this weren't in such way, Silanes simply wouldn't plan to increase in 42% its production of treatments for diabetes the following year, this could be equivalent to 850 millions of tablets.

And what can we say over benefits received for the Brasilian Aché, who allowed to introduce in the South American and Mexican market to fight cardiovascular diseases and diabetes.

The oral anti-diabetic market is valuated in more than 145 millions of dollars with an annual displacement of 20 millions of units in private sector.

Apart from being conquered a Brazilian pharmaceutical market that displaces about 1 thousand and 4 hundred millions of units a year, 40% more of National market.

After all, the reality is that Silanes is taking the steps that no other Mexican laboratory has been able to take in the medical world, where very important advances such as biotechnology and research, since several years before, are part of the reason to be.

So, we must to follow the clue to this Mexican laboratory that is in the top and goes with all to fight against a crisis that will affect many companies but also is an opportunity for other companies, and Laboratorios Silanes is one of the last that will continue to pave the way.

Exhibit E7

MONITOREO MEDIOS IMPRESOS

LABORATORIOS SILANES

Medio	Autor	Palabras clave	Fecha
El Norte	Palmira González	Laboratorios Silanes, Glimetal	25-noviembre-08

Venderá transnacional medicamento mexicano

› Dan a Sanofi-Aventis licencia para distribuir medicina para la diabetes desarrollada en México

Palmira González

Por primera vez en México, una medicina desarrollada en el País es licenciada a un laboratorio transnacional para su venta a nivel mundial.

El laboratorio mexicano Silanes desarrolló el llamado Glimetal —una medicina para el control de la diabetes tipo II—, y por un convenio de transferencia de tecnología se asocia con Sanofi-Aventis para lanzar el medicamento con una segunda marca, Amaryl-M.

Bajo este convenio, Glimetal seguirá siendo vendido en el País por Silanes, pero tendría acceso al mercado internacional a través de Sanofi-Aventis, informaron Nicolás Cartier, director general de Sanofi-Aventis en México, y Antonio López de Silanes, presidente de Laboratorios Silanes.

"Es la primera vez que hacemos una licencia en base a un producto desarrollado aquí en México", aseguró López.

En Estados Unidos es un proceso común que laboratorios pequeños o universidades desarrollen moléculas o sales con potencial de mercado y así atraigan a grandes laboratorios para comercializarlos.

En México no sucede así aún.

"Una de las razones por las que no hay tantos convenios es que hay pocos laboratorios haciendo desarrollos originales", consideró López.

López añadió que hay buenos centros de investigación en el País, pero falta aterrizar los proyectos a la realidad del mercado.

Silanes invierte actualmente un 10 por ciento de sus ventas —que rondan los mil millones de pesos al año— en investigación y desarrollo.

Entre otros de sus desarrollos exitosos está un antiveneno para alacrán, que se vende ya en todo el mundo, aunque no por convenios de licencias.

En este caso, Glimetal tiene ventas en México de entre 250 y 300 millones de pesos al año y para el 2009 podría sumar ya ventas en países como Colombia, Venezuela y otros países latinoamericanos.

Sanofi tendrá responsabilidad por comercializar el producto en los países donde Silanes no tenga presencia, dijo Cartier.

Los países donde Sanofi-Aventis ya identificó potencial de mercado están en América Latina, exceptuando Brasil; y los países grandes en África y Medio Oriente, abundó.

Para acceder a ellos iniciarán un estudio clínico en 30 países que les permitirá registrar el producto ante las autoridades sanitarias de esos mercados.

Este producto para Sanofi-Aventis no representa una participación importante en ventas pero sí un producto que complementa áreas estratégicas para mercados como el mexicano, de diabetes y oncología.

En la rama de diabetes, el producto más vendido de Sanofi-Aventis es la insulina Lantus, le sigue otro tipo de insulina Sibornat y la pastilla Amaryl.

Actualmente, Sanofi-Aventis tiene ventas a nivel mundial de 40 mil millones de dólares y en México unos 780 millones de dólares.

¿De dónde surge?

El Glimetal, la medicina desarrollada por el laboratorio mexicano Silanes para el control de la diabetes tipo II, tiene su origen en dos sustancias ya descubiertas.

› La glimepirida es una sal desarrollada en los 90 por el laboratorio Hoechst, que ahora pertenece a Sanofi-Aventis.

› La metformina es el primer medicamento ingerido para la diabetes.

› Ambas, explicó Silanes, eran sales que ya habían vencido en patente.

› El producto de Silanes es una combinación –patentada– de estas sales en la misma tableta.

› La tecnología desarrollada por Silanes es que ambas sales funcionen en conjunto y realizó las pruebas clínicas para avalar el medicamento ante Cofepris.

› Silanes obtuvo el Premio Nacional de Innovación por este producto.

Fuente: Silanes

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MONITOREO MEDIOS ELECTRÓNICOS

LABORATORIOS SILANES

DÍA: Martes 25 de noviembre
MEDIO: Grupo Imagen
NOTICIERO: Imagen Empresarial
CONDUCTOR: Carlos Mota
EMISIÓN: 90.5 FM
COBERTURA: Nacional
HORA: 6:01 AM
DURACIÓN: 43 segundos

DÍA: Martes 25 de noviembre
MEDIO: Grupo Imagen
NOTICIERO: Imagen Informativa
CONDUCTOR: Pedro Ferriz de Con
EMISIÓN: 90.5 FM
COBERTURA: Nacional
HORA: 9:46 AM
DURACIÓN: 42 segundos

DÍA: Martes 25 de noviembre
MEDIO: Grupo Imagen
NOTICIERO: Imagen Informativa Tarde
CONDUCTORA: Adela Micha
EMISIÓN: 90.5 FM
COBERTURA: Nacional
HORA: 14:52 PM
DURACIÓN: 39 segundos

DÍA: Miércoles 26 de noviembre
MEDIO: Milenio Televisión
NOTICIERO: Milenio Negocios
CONDUCTOR: Carlos Mota
EMISIÓN: canal 120 de Cablevisión y Sky
COBERTURA: Nacional
HORA DE TRANSMISIÓN: 19:30 PM
HORA DE REPETICIÓN: 20:30 PM
DURACIÓN: 7 minutos
VOCERO: Ing. Guillermo Funes

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Communication Specialized in Pharma & Public Relations

Monitoring of printed media

Laboratorios Silanes

Means	Author	Words	Date
"El Norte"	Palmira González	Silanes Laboratories,glimetal	25-November-08

TRANSNATIONAL COMPANY WILL SELL MEXICAN MEDICINE

Where does it come from?

Glimetal, the medicine developed by the Mexican laboratory Silanes for the control and treatment of the type II diabetes, has its origin in two already discovered substances.

The glimepiride is a salt developed in the 90s by Hoechst laboratory, which now belongs to Sanofi-Aventis.

The metformin was the first medicine prescribed for diabetes.

Both, explained Silanes, were salts whose patents had already expired.

The Silanes product is a - patented -combination of these salts in one pill.

The technology developed by Silanes is such that both salts work together as a team and they made clinical assays to guarantee the medicine before Cofepris.

Silanes obtained the National Prize for Innovation for this product.

- **They give to Sanofi-Aventis the license to distribute a medicine for diabetes developed in Mexico**

Palmira Gonzalez

For the first time in Mexico, a medicine developed within the Country is licensed to a transnational laboratory for its sale at world-wide level. The Mexican Laboratory Silanes developed Glimetal- a medicine for the control of type II diabetes- and by an agreement of technology transference it has associated with Sanofi-Aventis to launch the medicine with a second trademark, Amaryl-M.

Under this agreement, Glimetal will continue being sold in the country by Silanes, but it will have access to the international market through Sanofi-Aventis, informed Nicholas Cartier, general director of Sanofi-Aventis in Mexico, and Antonio Lopez de Silanes, president of Silanes Laboratories.

"It is the first time that we make a license for a product developed here in México" assured Lopez.

In the United States it is a common process that small laboratories or universities develop molecules or salts with market potential and thus attract big laboratories to commercialize them.

In Mexico this does not happen yet.

"One of the reasons why these kind of arrangements don't take place is that are few laboratories doing original research", considered López.

López added that there are good research centers in the Country, but they still have to land the projects to the reality of the market.

Silanes at the moment invest a 10 percent of their sales- that go up to around one billion pesos a year-in investigation and development.

Among others of his successful developments there is an antidote for scorpion poison that is already sold around the world, although not through licensing agreements.

In this case, Glimetal sales in Mexico are among the 250 and 300 million pesos a year and in 2009 could already count sales in countries like Colombia, Venezuela and other Latin American countries.

Sanofi will have the responsibility of commercializing the product in countries where Silanes has no presence, said Carrier.

The countries where Sanofi-Aventis has already identified potential markets are located in Latin America, excepting Brazil; and the bigger countries in Africa and the Middle East, he added.

In order to gain access to these countries they will initiate clinical studies in 30 of them, which will allow them to register the product before the sanitarian authorities of these countries.

This product does not represent an important change in sales for Sanofi-Aventis but it is a product that complements strategic areas for markets like the Mexican, for diabetes and oncology.

In the diabetes branch, the best Sanofi-Aventis product soldis the Lantus insulin, followed by another type of insulin Shorant and the Amaryl tablet.

At the moment, Sanofi-Aventis has world-wide sales at 40 billion dollars and about 750 million dollars in Mexico.

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Communication Specialized in Pharma & Public Relations

Monitoring electronic media

Laboratorios Silanes

DATE: Tuesday 25, November
MEDIA: Grupo Imagen
NEWS: Imagen Empresarial
HOST: Carlos Mota
STATION: 90.5 FM
COVERAGE: National
HOUR: 6:01 AM
DURATION: 43 seconds

DATE: Tuesday 25, November
MEDIA: Grupo Imagen
NEWS: Imagen Informativa
HOST:Pedro Ferriz de Con
STATION: 90.5
COVERAGE: National
HOUR:9:46 AM
DURATION: 42 seconds

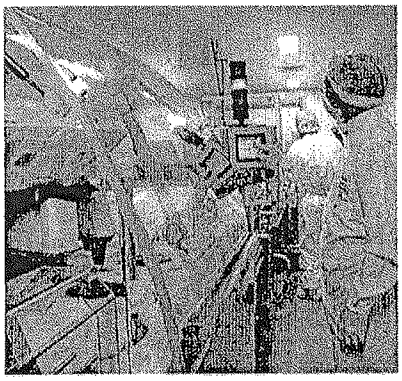
DATE: Tuesday 25, November
MEDIA: Grupo Imagen
NEWS: Imagen Informativa Tarde
HOST: Adela Micha
STATION: 90.5 FM
COVERAGE: National
HOUR: 14:52 PM
DURATION: 39 seconds

DATE: Wednesday 26, November
MEDIA: Milenio Television
NEWS: Milenio negocios
HOST: Carlos Mota
STATION: Channel 120 Cablevision and Sky
COVERAGE: National
HOUR: 19:30
DURATION; 7 minutes
SPOKESMAN: Ing. Guillermo Funes

Exhibit E8

Sunday, September 19, 2010

Negocios



Developing a New Market

With its entry into the Spanish market, the Mexican pharmaceutical company Silanes consolidates its status as a global player.

For over six decades, the history of pharmaceutical innovation in Mexico has been inextricably linked to Laboratorios Silanes. This company has led the way with its research and development work since it was founded in 1943 and it offers solutions in four areas: pharmachemicals, diagnostics, molecular biology and biotechnology, an area in which Silanes has been one of Mexico's pioneering companies.

"Around seven years ago, we had to decide which direction to take as a company: to stay within Mexico --producing generic drug products-- or to strike out internationally with innovative products [...] and we chose the latter road," recalls Antonio López de Silanes, CEO of Laboratorios Silanes and President of Grupo Silanes.

The company currently offers around 100 prescription drug products with a wide range of applications, ranging from treatments for diabetes, obesity, cardiovascular diseases and painkillers, as well as anti-inflammatories, analgesics, vitamins, antivenoms and diagnostic products. It produces 35 million treatment doses a year.

The company specializes in anti-diabetic drugs, offering the widest selection of oral therapeutic treatments for type 2 diabetes (DMT2), including Glimetal (glimepiride and metformin), holding the world's only patent for the drug. Its development earned it the Canifarma (National Chamber of the Pharmaceutical Industry) Award for Technological Research and Development in August 2008 and the ADIAT (Mexican Association of Directors of Applied Research and Technological Development) Prize for Technological Innovation in 2009. Oral anti-diabetics currently account for 50% of the company's sales, with an annual production of 1.5 billion tablets, which represent one-year treatment for one million people in Mexico, Central and South America.

To stay at the forefront of the local and international pharmaceutical industry, hard work and a commitment are needed, with new products constantly under development. "We invest 10% of our sales revenue into research," explains López de Silanes, "we have around 60 in-house and about 140 external researchers working in different centers around the world."

It has entered agreements with top academic institutions in Mexico, such as the National Autonomous University of Mexico (UNAM) and the National Institute of Nutrition (INNSZ), and in the US and Spain.

This has led to its registration of over 70 patents in Mexico, Europe and Central America and a presence in over 25 countries in Central and South America, the Caribbean, Europe, Africa and the Middle East.

Silanes now generates over 850 jobs directly and around 1,000 indirectly. The company is on the National Listing of Scientific and Technological Institutions and Companies (RENIECYT), issued by the National Council on Science and Technology (CONACYT) for companies involved in research and development work.

Its plant, located in the Toluca 2000 business park, in Estado de México, gives an example of its solid foundations for future growth. Opened in 2003, these premises with their state-of-the-art technology required an investment of 80 million usd. The plant received its Sanitary License from the Federal Commission for the Protection against Sanitary Risk (COFEPRIS) and was awarded, and re-awarded, a "Clean Manufacturing" certificate by the Federal Environmental Protection Agency (PROFEPA). Laboratorios Silanes has also implemented quality management systems at these installations, complying with the requirements of Good Manufacturing Practices and ISO 9001.

Next Stop: The World

Laboratorios Silanes is strongly motivated to reveal the quality and talent of Mexicans to the world. This explains its unstinting efforts to expand its international presence. This year it launched Glimetal throughout almost all of Latin America, in collaboration with two of its strategic partners: Aché Laboratorios Farmacéuticos, Brazil's largest pharmaceutical company, and the French company Sanofi- Aventis, both of which are widely recognized for their work on treatments for diabetes. This move has led to the export and marketing in 25 countries of a high-tech product developed entirely in Mexico.

To further extend its global reach, Laboratorios Silanes has now taken its second important step, this time toward Europe where it began operating in October 2009. The company will focus its strategy on research and development (R&D), working with its subsidiary Laboratorios Silanes IDF in Madrid with the aim of developing, registering and producing drug products for the global market.

This will require pre-clinical and clinical trials, approved by international organizations, with an estimated investment of 2 million euros over the next three years. The company has already begun its clinical research on four molecules focused on treating complaints related to metabolic syndrome. This research complies with the protocols and standards set out by the European Medicines Agency (EMEA).

"Spain is our portal into Europe," explains Antonio López de Silanes. "What is developed there can be sold throughout the EU and what is sold in the EU can be sold anywhere in the world. European certifications will open up strong new markets for us."

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